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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,758	01/18/2002	Thomas R. Cech	015389-002980US	6144

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,758	CECH ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-16,25-28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *1-8,25,27 and 28* is/are allowed.

6)☐ Claim(s) *9-16, 26, 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed August 22, 2006 in response to the Office Action of May 26, 2006 is acknowledged and has been entered. Previously pending claims 23-24, 29 have been cancelled and claims 30-31 have been added. Given that all product claims are now found allowable, claims 9-16, 26, 30-31 are rejoined with the currently allowable claims. Claims 1-16, 25-28, 30-31 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC 112

3. Claims 9-16, 26, 30-31 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method for detecting hTRT polypeptide, SEQ ID NO:225, does not reasonably provide enablement for a method of detecting (1) hTRT protein under conditions where an antibody forms a complex with a polypeptide comprising SEQ ID NO:225, (2) under conditions wherein the antibody binds to SEQ ID NO:67, (3) a fragment of hTRT protein (which reads on proteins comprising fragments of hTRT protein as small as 5 residues in length – the art recognized minimal epitope for antibody binding). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for detecting an undefined hTRT polypeptide. This means detecting non-functional splice variants (see below) as well as polypeptides comprising fragments of hTRT that are in fact not related in hTRT in either structure or function.

The specification teaches that "The present invention is directed to monoclonal or recombinant antibodies or fragments thereof that bind to human telomerase reverse transcriptase (hTRT) protein. The present invention is also directed to methods of identifying or detecting hTRT polypeptides in biological samples. The invention is further directed to methods of generating antibodies that specifically bind to hTRT protein (see abstract). The only other teaching drawn to hTRT in the specification is drawn to the elucidation of SEQ ID NO:225 and is found in the originally filed claims drawn to antibodies that bind to hTRT, SEQ ID NO:225, method of detecting unidentified hTRT proteins and methods of making antibodies to hTRT using amino acid sequences from SEQ ID NO:225 (see originally filed claims).

One cannot extrapolate the teaching of the specification to the scope of the claims because (1) the art recognizes that the human TRT protein includes proteins encoded by splice variants of the human TRT gene and the unpredictability of the function of splice variants is well known in the art, (2) the claims are drawn to the detection of undefined fragments of hTRT which read on fragments of as little as 5 amino acids that are comprised within polypeptides with neither structure nor function related to hTRT.

As drawn to the first aspect, post filing reference Yi et al (Nucleic acids Research, 2001, 23:4818l-4825) specifically teaches that human telomerase reverse transcriptase can be alternatively spliced into a variety of non-functional forms (see abstract). In addition, post-filing reference Krams et al (Am. J. Pathol., 2001, 159:1925-1932) specifically teaches that differential splicing of human telomerase reverse transcriptase has been demonstrated in various tissues and that it has been suggested that only full-length transcripts translate into functionally active

telomerase (see abstract). Further, Ohyashiki et al (Brit. J. Can., 2005, 92:1942-2947) specifically teaches that it has recently been discovered (in 1998, one year post filing of the priority document of the instant application) that alternative splicing of the human telomerase reverse transcriptase transcript is one of the regulatory mechanisms of telomerase activity and that several splice variants have been identified. (see p. 1942, col 1).

Given the clear teachings that human TRT include numerous splice variants, many of which are nonfunctional, one would not know how to use the hTRT "detected" by the claimed methods in particular because the art recognizes the unpredictability of the function of splice variants. For example, Hirashima (Int. Arch. Allergy Immunol., 2000, Suppl 1:6-9)) discloses that there are multiple isoforms of ecalectin/galectin-9 (page 8, first column second paragraph, lines 10-16), and "it cannot be excluded that each isoform exhibits different biological activity" (page 8, second column, lines 6-7). Benedict et al (J. Exp. Medicine, 2001, 193(1)89-99) specifically teach that two splice isoforms of terminal deoxynucleotidy transferase (a long form and a short form) enter the nucleus but have different activity, the long form does not catalyze nontemplated nucleotide addition but rather modulates the activity of the short form (see abstract). Jiang et al (JBC, 2003, 278(7) 4763-4769 specifically teach that the type 3 Ca2+ release channel, RyR3 exhibits strikingly different pharmacologic and functional properties depending on the tissues in which it resides. Upon examination, seven tissue specific alternatively spliced variants of RyR3 were detected. One of the variants was unable to form a functional channel but was able to suppress the activity of a different release channel. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the

pharmacologic and functional heterogeneities of RyR3 (see abstract). Finally, the references drawn to hTRT above clearly disclose multiple non-functional splice variants. These references serve to demonstrate that one of skill in the art cannot predict the biological activity of splice variants based on the biological activity of the wild-type protein or a single protein isoform.

Given that the claims are drawn to detecting "hTRT" with an antibody, given that it is understood by those of ordinary skill in the art that antibodies that recognize proteins bind to epitopes of varying size, and a grouping of the order of about four or five amino acids, contiguous or not, is regarded as a typical number of amino acids in a minimal epitope. See, e.g., Nair et al., J. Immunol 2000 165(12): 6949-6955 and given that the phenomenon of cross reactivity is well known in the art wherein Roitt et al (Immunology, 1993, Mosby, St. Louis, p 6.4-6.5) specifically teach that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B, it is clear that any antibody that binds to SEQ ID NO:225 will also bind to any other protein that shares amino acid residues with the epitope bound by said antibody. Thus, any splice variant isoform that binds to an antibody that is also bound to SEQ ID NO:225 will be "detected" by the claimed methods. However, neither the specification nor the art at the time the invention was made taught how to predictably distinguish those "hTRT" that function as hTRT from those that do not or how to use the detected "hTRT" that are not functional hTRT.

As drawn to the second aspect, the art recognizes the unpredictability of the protein chemistry arts. In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into

unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, it could not be predicted, nor would it be expected that a polypeptide comprising as little as 5 amino acids in common with SEQ ID NO:225 would have significant structure or function in common with SEQ ID NO:225 and one would not know how to use the detected protein.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the detected proteins with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

New Grounds of Objection

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). However, since the claims as filed in the original specification are part of the disclosure and therefore, if an application as originally filed contains a claim disclosing material not disclosed in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. In re Benno, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985).

The claims lacking antecedent basis are claims 1-16, 25-28, 30-31. Appropriate correction is required.

5. Claims 1-8, 25, 27-28 are allowable.

6. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

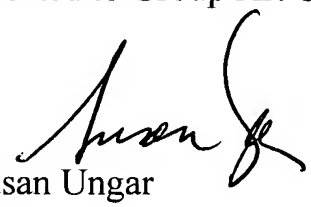
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT

TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
October 20, 2006